AMENDED SPECIFICATION

Reprinted as amended in accordance with the Decision of the Superintending Examiner acting for the Comptroller General dated the twenty-eighth day of April, 1967, under Section 14, of the Patents Act, 1949.

PATENT SPECIFICATION

924539

NO DRAWINGS

924539

Date of Application and filing Complete Specification: Sept. 20, 1961.
No. 33735/61.
Application made in Japan (No. 39264) on Sept. 20, 1960.
Application made in Japan (No. 30819) on Aug. 25, 1961.
Complete Specification Published: April 24, 1963.

Index at acceptance:—Class 2(3), V.

International Classification:—C07d.

COMPLETE SPECIFICATION

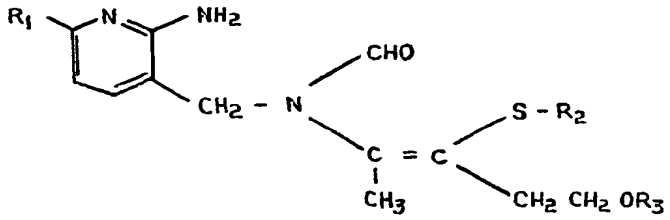
Thiamine Derivatives

We, SHIONOGI & CO. LTD., a Japanese Body Corporate, of 12, 3-chome, Dosho-machi, Osaka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to thiamine derivatives, particularly S - (substituted - oxycarbonyl) - thiamines, and to processes for their preparation.

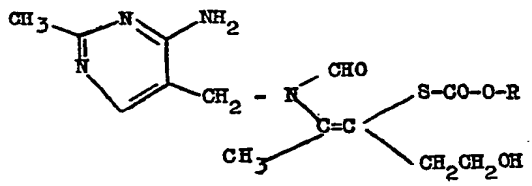
Thiamine derivatives having better characteristics for therapeutic and hygienic purposes have been studied previously by several laboratories. Among these thiamine propyl disulfide is known for its good intestinal absorption. We have studied thiamine derivatives and recently succeeded in obtaining thiamine derivatives having better characteristics than thiamine propyl disulfide.

The Applicants are also aware of Patent Specification No. 741,250 which describes thiamine derivatives of the general formula:



where R_1 represents methyl or ethyl, R_2 an acyl group and R_3 hydrogen or an acyl group.

According to the present invention there is provided a process for preparing a compound of the formula:



BNSDOCID: <GB_____924539A_1_>

wherein R represents a hydrocarbon group having 1 to 12 carbon atoms or an alkoxyalkyl radical represented by the following formula:

$$CH_3(CH_2)_n—O—(CH_2)_m—$$

wherein m is an integer from 1—5 and n is an integer from 0—4, which process comprises reacting thiol-type thiamine with a compound having the formula:

$$(NO_2)_z - C_6H_4 - O-CO-O-R$$

wherein R is as hereinbefore defined and z is an integer from 1—3.

Among the compounds obtained by the inventors by processes in accordance with this invention, the following are the most useful.

S - Ethoxycarbonyl - thiamine; mp. 140°C (with decomposition).

Anal. Calcd. for $C_{15}H_{22}O_4N_4S$: C 50.83, H 6.26, N 15.81, S 9.05
Found: C 51.01, H 6.56, N 15.53, S 9.55.

Hydrochloride: m.p. 172—173°C (with decomposition).

S - Propyloxycarbonyl - thiamine; mp. 156—157°C (with decomposition).

Anal. Calcd. for $C_{16}H_{24}O_4N_4S$: C 52.15, H 6.57, N 15.21.
Found: C 52.21, H 6.94, N 14.87.

S - Isopropyloxycarbonyl - thiamine; mp. 157°C (with decomposition).

Anal. Calcd. for $C_{16}H_{24}O_4N_4S$: C 52.15, H 6.57, N 15.21
Found: C 51.97, H 6.84, N 15.01

Hydrochloride; mp. 173°C (with decomposition).

S - Butyloxycarbonyl - thiamine; mp. 139—140°C (with decomposition).

Anal. Calcd. for $C_{17}H_{26}O_4N_4S$: C 53.38, H 6.85, N 14.65, S 8.38.
Found: C 52.97, H 7.16, N 14.77, S 8.03.

Hydrochloride; mp. 169—170°C (with decomposition).

S - Isobutyloxycarbonyl - thiamine; mp. 142—143°C (with decomposition).

Anal. Calcd. for $C_{17}H_{26}O_4N_4S$: C 53.38, H 6.85, N 14.65, S 8.38.
Found: C 53.58, H 6.96, N 14.29, S 8.29

S - Isopentyloxycarbonyl - thiamine; mp. 134—136°C (with decomposition).

Anal. Calcd. for $C_{18}H_{28}O_4N_4S$: C 54.78, H 7.33, N 14.17, S 8.04.
Found: C 54.52, H 7.12, N 14.13, S 8.09.

S - Octyloxycarbonyl - thiamine; mp. 165°C (with decomposition).

Anal. Calcd. for $C_{21}H_{34}O_4N_4S.2H_2O$: C 53.14, H 7.86, N 11.81.
Found: C 53.03, H 7.56, N 12.01.

S - Cyclohexyloxycarbonyl - thiamine; mp. 152—154°C (with decomposition).

Anal. Calcd. for $C_{19}H_{28}O_4N_4S$: C 55.86, H 6.91, N 13.71.
Found: C 56.07, H 6.90, N 13.61.

BNSDOCID: <GB _____924539A_I_>

S - Allyloxycarbonyl - thiamine; mp. 135°C (with decomposition).

Anal. Calcd. for $C_{16}H_{22}O_4N_4S$: C 52.45, H 6.05.
Found: C 52.35, H 6.24.

S - Benzyloxycarbonyl - thiamine; mp. 140°C (with decomposition).

Anal. Calcd. for $C_{20}H_{24}O_4N_4S$: C 57.67, H 5.81, N 13.46.
Found: C, 57.28, H, 5.83, N, 13.53.

Hydrochloride: mp. 157—159°C (with decomposition).

S - Phenethyloxycarbonyl - thiamine; mp. 147°C (with decomposition).

Anal. Calcd. for $C_{21}H_{26}O_4N_4S$: C 58.59, H 6.09, N 13.02.
Found: C 58.67, H 5.74, N 12.89.

Hydrochloride: mp. 171—173°C (with decomposition).

S - (2 - Methoxyethoxycarbonyl) - thiamine; mp. 127—128°C (with decomposition).

Anal. Calcd. for $C_{16}H_{24}O_5N_4S$: C 49.48, H 6.29, N 14.57.
Found: C 50.15, H 6.43, N 14.55.

Changes in the level of vitamin B_1 in blood by oral administration of S - ethoxycarbonyl - thiamine and (shown in brackets) thiamine propyl disulfide were determined at 1, 3 and 5 hours after administration to rabbits (each dose 5 mg. per kg. of body weight) as the values of 70.0 (50.9), 81.2 (62.9) and 71.5 (52.3) by the unit of μg. per dl. of blood volume, and were determined also at 1 and 6 hours after administration to rats (each dose 50 mg. per kg. of body weight) as the values of 846 (456) and 351 (237) by the same unit as above. Similar test for gastrointestinal absorption on human subjects gave equally remarkable results. Thus, S - ethocycarbonyl - thiamine increases the level of vitamin B_1 in the blood from 7.08 to 27.35 while thiamine propyl disulfide increases the level from 7.19 to 15.82 (μg./dl.) at 3 hours after administration (each dose: 50 mg./man.). Acute toxicity (LD_{50} in mice, mg./kg.) was also determined as 12352 for S - ethoxycarbonyl - thiamine (3890 for thiamine propyl disulfide) *per os*.

S - Propyloxycarbonyl - thiamine increases the amount of vitamin B_1 in the blood to a higher level and more rapidly, than does thiamine propyl disulfide.

S - Isopropyloxycarbonyl - thiamine increases the amount of vitamin B_1 in the blood to a higher level than thiamine propyl disulfide does.

S - Butyloxycarbonyl - thiamine shows, like S - ethoxycarbonyl - thiamine, the particular property of being able to increase the amount of vitamin B_1 in liver and muscle to a higher level than thiamine propyl disulfide can. Thus, the former increases to 34.7 (1 hour after) and 23.3 (6 hours after) while the latter increases to 29.6 (1 hour after) and 20.1 (6 hours after) μg./g. of liver tissues using the dose of 50 mg./kg. of rat; and the former increases to 2.31 (1 hour after) and 2.09 (6 hours after) while the latter increases to 1.75 (1 hour after) and 1.80 (6 hours after) μg./g. of muscle tussues using the dose of 50 mg./kg. of rat. This increases the level of vitamin B_1 in blood as high as S - ethoxycarbonyl - thiamine does.

S - Isobutyloxycarbonyl-, S - isopentyloxycarbonyl- and S - benzyl - oxycarbonyl - thiamine are excellent for the maintenance of the amount of vitamin B_1 in blood of rabbits at a higher level than thiamine propyl disulfide.

S - Cyclohexyloxycarbonyl - thiamine increases the level of vitamin B_1 in the blood by as much and as rapidly as S - propyloxycarbonyl - thiamine does.

S - (2 - Methoxyethoxycarbonyl) - thiamine and S - Phenethyloxycarbonyl - thiamine are as effective as S - isopropyloxycarbonyl - thiamine in this respect, and far more effective than thiamine propyl disulfide.

S - Allyloxycarbonyl - thiamine is even better in this respect than the above mentioned four compounds. The level of vitamin B_1 in the blood of rabbits is increased to 86.3 (3 hours after administration) and 54.8 (8 hours) while thiamine propyl disulfide

increases to 62.9 and 39.7 (same condition) μg./dl. of blood using the dose of 5 mg./kg. of body weight. Gastro-intestinal absorption of this compound on human subjects (50 mg./man) is equally high, thus, this compound increases the level of vitamin B_1 in the blood from 6.70 to 20.97 while thiamine propyl disulfide increases it from 7.19 to 15.82 (μg./dl.) at 3 hours after administration.

These thiamine derivatives are all stable to aneurinase, like thiamine propyl disulfide.

The practical procedures in carrying out the processes in accordance with the present invention are essentially the same whichever S - (substituted - oxycarbonyl) - thiamine is to be prepared.

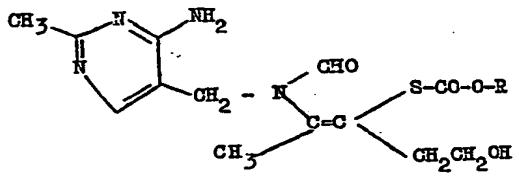
The practical procedures for S - ethoxycarbonyl - thiamine are illustrated as an example. For this reason, the methods of synthesising these compounds are not to be confined by the following.

EXAMPLE

In a solvent consisting of 50 ml. of ethanol, 3.6 g. of sodium salt of thiol-type thiamine and 2.6 g. of 2,4 - dinitrophenyl ethylcarbonate are reacted under reflux for 1.5 hours. After chilling, suspensoids are removed by filtration and the filtrate is concentrated, thereby 2,4 - dinitrophenol separates out. The mixture is filtered and the filtrate is concentrated and evaporated almost to dryness. The residue is dissolved in a small volume of water and the resulting solution is extracted with ethyl acetate. The extract is subjected to counter-extraction with 5% HCl and the resulting acidic solution is neutralized with sodium bicarbonate solution. Then the obtained alkaline solution is extracted with chloroform and, after drying over anhydrous Na_2SO_4, the extract is evaporated, thereby 2.6 g. of crude crystalline product is obtained. This affords pure S - ethoxycarbonyl - thiamine as colourless cubic crystals of mp. 140°C (with decomposition) by re-crystallization from an ethanol-ethyl acetate mixture (1 : 1).

WHAT WE CLAIM IS:—

1. A process for preparing a compound of the formula



wherein R represents a hydrocarbon group having 1 to 12 carbon atoms or an alkoxyalkyl radical represented by the following formula

$$CH_3(CH_2)_n—O—(CH_2)_m—$$

wherein m is an integer from 1—5 and n is an integer from 0—4, which process comprises reacting thiol-type thiamine with a compound having the formula

wherein R is as hereinbefore defined and z is an integer from 1—3.

2. A process as claimed in claim 1, substantially as hereinbefore described with reference to the Example.

3. S - (Substituted - oxycarbonyl) - thiamines whenever prepared by the process claimed in claim 1 or in claim 2.

SHIONOGI & COMPANY LIMITED,
Per: Boult, Wade & Tennant,
111/112, Hatton Garden,
London, E.C.1.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.
—1967. Published by The Patent Office, 25 Southampton Buildings, London, W.C.2,
from which copies may be obtained.